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R E M A R K S

Claims 47-68 are pending in the instant application. The Examiner has objected to the specification under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure and as requiring undue experimentation. Claim 62 stands rejected under section 112, first paragraph, as lacking the support of an enabling disclosure. Claims 54 and 55 stand rejected under 35 U.S.C. § 112, fourth paragraph, as being of improper dependent form. Claims 47-68 stand rejected under 35 U.S.C. § 103 as being unpatentably obvious over Cousens et al (1A, of record) in view of the Cohen et al. patent (1B, of record).

Applicants have amended claims 47 and 64 to more precisely define the claimed inventions. No new matter is introduced by these amendments. Additionally, Applicants hereby cancel claims 54, 55, and 62 without prejudice. To the extent that the Examiner's rejections apply to the claims as amended herein, Applicants respectfully traverse the rejections for the reasons set forth below.

Explanation of the instant invention

As defined by the newly amended claims, Applicants' invention is a fused polypeptide which comprises a combination of distinct, separate amino acid sequences. Said combination endows the overall fused polypeptide with intrinsic operativeness not associated with any one of its distinct component parts. This intrinsic operativeness is a direct consequence of the structural and conformational features imparted to the fused polypeptide by said combination. Applicants refer the Examiner to Figure 2 of their application for a pictorial representation of one of the combinations contemplated by Applicants' invention, and the structural and conformational features which directly result from

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said representative combination. Important to an appreciation of the instant invention's patentability is understanding that eventual recovery of that component of said fused polypeptide known as the selected target polypeptide is directly facilitated by the fused polypeptide's structural and conformational features. In essence, Applicants' invention is a combination of separate, distinct amino acid sequences which together endow the fused polypeptide with structural and conformational features critical to operativeness.

As defined by the amended claims, the instant invention is far more than a fusion polypeptide employing a selectively cleavable link at which an enzymatic cleavage agent acts to selectively cleave a precursor polypeptide. A critical point is that Applicants' cleavage site alone is not that feature of Applicants' invention which imparts operativeness. Rather, Applicants' combination of a distinct hinge region together with a cleavage site operates to permit ready release of said target polypeptide from the precursor polypeptide upon treatment with an enzymatic cleavage agent. This type of physico-chemical cooperation between said cleavage site and said hinge region of the instant invention is precisely articulated in the amended claims. The combination of a distinct hinge region with a particular cleavage site within the claimed fused polypeptide serves to present the fused polypeptide to the enzymatic cleavage agent such that preferential cleavage at the cleavage site occurs. Consequently, relative to prior art fusion proteins, recovery of intact, uncleaved target polypeptide is significantly facilitated.

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Rejection of Claim 62, and Objection to the Specification, Under
35 U.S.C. § 112, First Paragraph

Claim 62 stands rejected, and the specification is objected to, under section 112, first paragraph. Applicants have cancelled without prejudice claim 62, thereby obviating the continued applicability of these issues to the instant application.

Cousens et al. U.S.S.N. 06/717,209 as Prior Art

Background

For all the reasons stated in Applicants' previous paper filed on December 27, 1993, Applicants disagree with the Examiner's continued characterization of the Cousens et al. abandoned, parent application Serial No. 06/717,209 [hereinafter referred to as '209] as a prior art reference for the purposes of section 103. As discussed previously, Applicants firmly believe that use of the Cousens et al. '209 reference as prior art is contrary to the holding of the Court of Customs and Patent Appeals in In re Wertheim, 646 F.2d 527 (C.C.P.A. 1981).

Before repeating the substance of their legal objection, Applicants again wish to review the pertinent prosecution events in the instant case. During prosecution of the instant application, Applicants swore behind the filing date of the Cousens et al. continuation-in-part patent U.S. 4,751,180 [hereinafter referred to as '180] which derived from the abandoned Cousens et al. '209 reference. By so doing, Applicants successfully eliminated the continuation-in-part patent as a prior art reference. But, by applying a relation-back principle purportedly pursuant to 35 U.S.C. § 120, the Examiner ruled that the abandoned Cousens et al. '209 parent application would remain in the instant case as prior art under section 102(e) for section 103 purposes since the '209 reference antedated Applicants'

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declaration. In essence, the inventors of the patentable subject matter in U.S. '180 were afforded the exclusionary benefit of the abandoned parent application's earlier filing date under the auspices of section 120. Thus, according to the Examiner's reasoning, Applicants must now demonstrate that the instant invention is patentably unobvious over the Cousens et al. '209 prior art reference.

The applicable law: In re Wertheim (C.C.P.A. 1981)

The circumstances under which the relation-back principle of section 120 may be applied are carefully described in In re Wertheim. In Wertheim the court addressed the issue of when a patent is entitled to the benefit of the filing date of a remote application. Specifically, the court stated that "an abandoned application by itself can never be a reference." Id. at 535. According to Wertheim, the critical legal issue is whether the invention claimed in the subsequent patent finds a supporting disclosure in compliance with section 112, as required by section 120, in the abandoned application so as to entitle that invention to the filing date of the abandoned application for prior art purposes. Id. at 537. If the disclosures of the remote application do not fully support a claim in the patent, or if the claims of the subsequent patent derive essential support from new matter added by later continuation-in-part applications, then it is not effective for prior art purposes under section 102(e) and 103 as of the remote filing date. This is true even though the disclosed matter in question appeared in the remote application and is carried forward into the patent. In this regard, the court stated:

We emphasize that the above noted statutes, §§ 102(e), 120, and 112, speak with reference to some specific claimed subject matter It is axiomatic in patent law that questions of description, disclosure, enablement, anticipation, and obviousness can only be discussed with reference to a specific claim which identifies "the invention" referred to in the statutes.

Thus, the determinative question here is whether the invention claimed in the [subsequently issued patent] finds a supporting disclosure in compliance with § 112, as required by § 120, in the [remote application] so as to entitle that invention in the [subsequent patent], as "prior art," to the filing date of [the remote application]. Without such support, the invention, and its accompanying disclosure, cannot be regarded as prior art as of that filing date.

Id. at 537 (emphasis added).

Furthermore, Wertheim criticized and accordingly modified two earlier cases which relied merely on the fact that disclosures in remote or abandoned applications had been "carried over" to later applications as satisfying section 120. (The two modified cases are In re Switzer, 166 F.2d (C.C.P.A. 1948) and In re Lund, 376 F.2d 982 (C.C.P.A. 1967), both of which are cited at page 900-1 of the MPEP (Nov. 14 1992).)

Application of the legal standard of *In re Wertheim* to the instant case

Wertheim is particularly relevant to the instant case which involves an abandoned parent application and the continuation-in-part patent derived therefrom. As pointed out by Wertheim, new matter can add material limitations which transform an unpatentable invention into a patentable one. A continuation-in-part application does not necessarily insure that all critical aspects of the later application were present in the parent. Thus, in such a situation, only a remote application disclosing the patented invention as required by section 112 before the addition of new matter can be relied upon to give the subsequent patent the benefit of the earlier filing date for the purpose of supporting a section 102(e)/103 rejection. Id.

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Comparison of the disclosures of the '180 continuation-in-part patent and its '209 abandoned parent application

Given that the Examiner and Applicants disagree, Applicants will discuss in detail the critical differences between the two references.

As was the case in Wertheim, there are claim limitations in the Cousens et al. '180 patent missing from the Cousens et al. '209 parent application. For example, Applicants refer the Examiner to issued claims 16, 19, and 20-22 in the Cousens et al. '180 patent reference. These are the claims which define the patentee's "hinge amino acids" and fusion proteins containing such amino acids. These claims are absent from the '209 abandoned parent application.

Also absent from the '209 parent is any supporting specification for such claims. Applicants request that the Examiner compare the Table on page 15 and the specification on page 5 of the abandoned parent application, with column 4 and Table 1 of the issued continuation-in-part patent. Specifically, at column 4, lines 16-48, the '180 continuation-in-part specification recites the following new matter:

In addition to the amino acids comprising the cleavable site, it may be advantageous to separate further the two fused polypeptides. Such a "hinge" would allow for steric flexibility so that the fused polypeptides would be less likely to interfere with each other, thus preventing incorrect folding, blockage of the cleavage site, or the like.

The "hinge" amino acid sequence could be of variable length and may contain any amino acid side chains so long as the side chains do not interfere with the mode of action employed to break at the cleavable site Preferably the amino acids comprising the hinge would have side chains that are neutral and either polar or nonpolar and may include one or more prolines. The hinge region will have at least one amino acid
. . . .

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So that the "hinge" amino acids are not bound to the final cleaved polypeptide of interest, it is desirable, but not required to practice the invention, to place the "hinge" between the polypeptide that is produced independently at high yield and the sequence for the cleavable site. (Emphasis added)

Corresponding to this new matter are numerous new experimental entries in Table 1 of the '180 continuation-in-part (Table 1 appears at column 10). In fact, these new entries are specifically labeled as "hinge" to distinguish them from the original entries which do not illustrate SOD-Met-Proinsulin fusion proteins characterized as containing a "hinge." Additionally, the data in Table 1 summarize the experiments of Examples II through III which appear at columns 12 to 17 of the continuation-in-part patent, but are absent from the specification of the '209 abandoned parent application. Clearly, in view of this evidence, the Examiner can not reasonably continue to assert that the '180 continuation-in-part patent derives the benefit of its abandoned parent's earlier filing date. The '180 patent expressly distinguishes the new "hinge" matter from the originally-submitted matter because no "hinge" matter was, in fact, contained within the originally-submitted application.

Furthermore, Applicants submit that, upon reading the '180 continuation-in-part patent, it is clear that the above-referenced claim limitations and corresponding new matter is a necessary part of the patentable invention as set forth in the issued continuation-in-part patent. These limitations and new matter, however, are neither expressly nor inherently part of the Cousins et al. '209 parent application. Thus, absent these limitations and new matter, reliance on the earlier filing date and use of the '209 reference as prior art is not legally permissible and in direct contravention of the Wertheim rule.

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Without the benefit of the earlier date, Applicants previously submitted declaration is sufficient to eliminate consideration of any Cousens et al. reference, in whole or in part, as prior art to be combined with another reference to support a section 103 rejection. Thus, Applicants respectfully submit that the claims as amended are in condition for allowance.

Rejection of Claims 47-68 under 35 U.S.C. § 103

The Examiner has rejected claims 47-68 under 35 U.S.C. § 103 as being unpatentable over Cousens et al. in view of Cohen et al. In view of the above discussion of In re Wertheim, the Cousens et al. '209 reference must be removed as a prior art reference in the instant case, thereby obviating the Examiner's section 103 rejection. Even if the Examiner continues to rely upon the Cousens et al. '209 reference as prior art for purposes of section 103, however, Applicants believe that the instant invention is patentable over Cousens et al. in view of Cohen et al. for the following reasons. The Examiner's section 103 rejection is discussed below in the context of the amended claims.

As defined by the amended claims, the instant invention is far more than a fusion polypeptide employing "a selectively cleavable link," as disclosed in the Cousens et al. '209 parent application, at which an enzymatic cleavage agent acts to selectively cleave a precursor polypeptide. A critical distinction between the Cousens et al. '209 disclosure and Applicants' invention is that Applicants' cleavage site alone is not that feature of Applicants' invention which imparts operativeness. Rather, Applicants' combination of a distinct hinge region together with a cleavage site operates to permit ready release of said target polypeptide from the precursor polypeptide upon treatment with an enzymatic cleavage agent. This type of physico-chemical cooperation between said cleavage

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site and said hinge region achieved by the instant invention is precisely articulated in the amended claims. No such teaching or suggestion of an operative combination of a distinct cleavage site and a distinct hinge region appears in the Cousins et al. '209 parent application. The combination of a distinct hinge region with a particular cleavage site within the claimed fused polypeptide serves to present the fused polypeptide to the enzymatic cleavage agent such that preferential cleavage at the cleavage site occurs. Consequently, recovery of intact, uncleaved target polypeptide is significantly facilitated. No such teaching or suggestion concerning operativeness can be found in the Cousins et al. '209 parent application. This feature of Applicants' claimed combination further supports the conclusion that their invention is patentably unobvious over the Cousins et al. '209 parent application.

The final Office Action states that the '209 reference implicitly teaches a hinge-like flexible structure which promotes cleavage. Similarly, it further states that artisans like Cousins et al. would have appreciated use of a flexible linker without explicitly stating so. Applicants respectfully point out that it is a well-settled legal principal that in order for a rejection to be based upon a property that is inherent in the prior art, such inherency must be necessary and certain. In Interchemical Corp. v. Watson, 145 F. Supp. 179, 182 (D.D.C. 1956), aff'd 251 F.2d 390 (D.C. Cir. 1958), the court stated that "[t]he law requires that inherency may not be established by possibilities or probabilities. The evidence must show that the inherency is necessary and inevitable."

Given the subject matter of the Cousins et al. '209 disclosure, the necessary and certain legal standard can not be met. There is no basis for properly concluding that a flexible, hinge-like structure with the operativeness claimed by Applicants is a necessary and certain consequence of the Cousins et al.

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disclosure. The references supplied by the Examiner (Lehninger and Lofdahl) do not, in the opinion of Applicants, speak to this issue. Furthermore, as stated above, Cousens et al. failed to even recognize the problem solved by Applicants, and contained no teaching or suggestion of the claimed combination of elements or the unexpected results obtained in using it.

The proper standard for a rejection under section 103 is set out in Graham v. John Deere Co., 148 U.S.P.Q. 459 (S.Ct. 1966). In order for an obviousness rejection under section 103 to be proper, the Examiner must show that the essential elements defined by the Applicants' claims as they relate to the "subject matter as a whole" are taught or suggested by the cited art. In the case of the instant invention, it is Applicants' claimed combination which is inventive. Applicants' amended claims define a combination of distinct and separate amino acid sequences which endows the overall fused polypeptide with certain conformational and structural features operable to facilitate selective recovery of a target polypeptide. Such a combination is neither taught nor suggested by the prior art.

Under the proper standard for obviousness, every attempt at showing a *prima facie* case of obviousness must show cognizance of all of the differences between the claimed subject matter and the prior art, as well as for the effect those differences create. Id. at 467. The differences between Applicants' claimed subject matter and the Cousens '209 reference were discussed above. These differences would not have been obvious to one skilled in the art because the cited references do not teach, suggest, or motivate one to practice the Applicants' claimed combination invention.

Cohen et al. U.S. 4,743,679 [hereinafter referred to as '679] teaches that the elimination of cysteine residues in a leader-type peptide prevents possible interactions and

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interferences with the obligatory formation of disulfide bridges. The Examiner suggests that this teaching, in view of Cousens et al., renders Applicants' claimed combination unpatentably obvious. Applicants believe that the Examiner's rejection is predicated upon an improper combination of the Cousens et al. '209 reference with the Cohen et al. '679 reference. The law of combination of references is clearly stated in Eversharp, Inc. v. Fisher Pen Co., Inc., 132 U.S.P.Q. 423 (N.D.Ill. 1961):

In order for one to defeat a meritorious patent it is not enough to pick out isolated features in earlier prior art patents, combine them in one particular way with hindsight acquired only from the patent under attack, and then say that no invention would have been involved in selecting those particular features and combining them in the particular way in which the patentee did.

In fact, in citing this Eversharp case, the district court in Matherson-Selig Co. v. Color Card, Inc., 154 U.S.P.Q. 265 (N.D.Ill. 1967) stated:

References may be combined to establish obviousness, but they must suggest the combination itself and not merely all of the elements which make up the combination, for it is the combination and not the individual elements that comprise the invention.

The claimed combination is unique and achieves results that would not have been obvious to a skilled artisan relying solely upon Cousens et al. with or without Cohen et al., since neither reference recognized the problem solved by Applicants. One skilled in the art relying upon these reference would not have been motivated to combine them because the Cousens et al. and Cohen et al. references, taken singly or combined, do not teach or suggest the combination of separate and distinct amino acid sequences which comprises the Applicants' claimed subject matter as a whole, nor the advantages obtained thereby. Furthermore,

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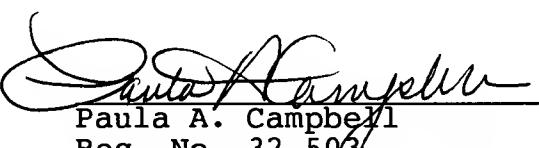
neither Cousins et al. or Cohen et al. provides the required teaching, suggestions, or incentive which would have led one of ordinary skill in the art to combine the relevant teachings of the references.

Conclusion

In view of the above, Applicants request reconsideration and allowance of the amended claims. If the Examiner believes that a discussion with Applicants' attorney would expedite prosecution of the instant application, the Examiner is urged to telephone the undersigned at 617-248-7263.

Respectfully submitted,

Date: June 17, 1994


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